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HOT-MELT EXTRUDABLE PHARMACEUTICAL FORMULATION

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(57) Abstract

The present invention relates to pharmaceutical formulations comprising a hot-melt extrudable mixture of a therapeutic compound and a high molecular weight poly(ethylene oxide). In some embodiments, the formulation further comprises poly(ethylene glycol). The present invention also includes methods for hot-melt extruding pharmaceutical formulations.

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HOT-MELT EXTRUDABLE PHARMACEUTICAL FORMULATION

The application claims priority to United States Patent Application Serial No. 60/020,623, filed June 26, 1996.

FIELD OF THE INVENTION

The present invention relates to poly(ethylene oxide) (PEO) based hot-melt extrudable pharmaceutical formulations. The invention relates more specifically to formulations which have been prepared by hot-melt extrusion of mixtures containing high molecular weight PEO and a therapeutic compound for use in controlled-release drug delivery.

BACKGROUND OF THE INVENTION AND DESCRIPTION OF THE PRIOR ART

Controlled-release pharmaceutical formulations comprising PEO and a therapeutic compound are known in the art. Those formulations generally have PEO as a minor component and require other components in order to render the formulation a controlled release one.

Hot-melt extrusion as a method for producing polymer-based sustained-release pharmaceutical formulations, such as with derivatized cellulose, poly(methacrylate) derivative, poly(ethylene-co-vinyl acetate), poly(ethylene), poly(vinyl acetate-co-methacrylic acid), epoxy resins and caprolactones is known. These methods do not teach the use of poly(ethylene oxide).

Hot-melt extrusion as a method for producing poly(ethylene glycol) based pharmaceutical formulations comprising an "erosion rate modifier" has been disclosed. These particular compositions have been described as further containing trace amounts of high molecular weight PEO, and the hot-melt extrusion process used to prepare them requires several steps. These particular compositions are also based upon a low melting matrix drug delivery system, are predominantly for sublingual and transdermal rather than oral administration and are not long acting sustained release formulations.

Alderman et al. (EP 0177893 A2) discloses "a thermoformable sustained release matrix for the prolonged release of an active organic material" comprising "a thermoplastic water-soluble gel having a water-soluble hydroxypropylmethylcellulose,"

a plasticizer and "an effective amount of an active organic material dispersed in said gel." The plasticizer may be a low molecular weight poly(ethylene glycol).

Mooney et al. (EP 0598606 A1) relates to "compositions comprising a thermoplastic water-soluble polymer; a water-soluble polymer derived from a carboxylic acid or a pharmaceutically acceptable salt thereof; and a plasticizer." The thermoplastic water-soluble polymer may be poly(ethylene oxide), and the compositions can be prepared as hot melts.

The primary drawback of these various methods has been the requirement of several components to achieve the desired controlled release profile and the potential for loss in pharmacological activity of the included therapeutic agent.

Hot-melt extrusion processes in the art have generally required elevated temperatures, and for that reason, which could cause decomposition of the therapeutic agent or polymer matrix used in the formulation. Hot-melt extrusion of high molecular weight PEO mixed with a therapeutic compound is not known in the art.

It has not been appreciated that a high molecular weight PEO based therapeutic compound containing composition can be hot melt extruded without significant degradation or decomposition of either the PEO or therapeutic compound.

Although various hot-melt extrusion pharmaceutical formulations and methods for making them are known, development of simple formulations for drug delivery and methods for producing them remains a problem to the pharmaceutical industry.

Accordingly, there is a need to develop simple controlled-release pharmaceutical formulations and simple methods for their preparation.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide a hot-melt extrudable controlled-release pharmaceutical formulation comprising high molecular weight poly(ethylene oxide) and an effective amount of a therapeutic compound.

It is another object of the present invention to provide a hot-melt extrudable controlled-release pharmaceutical formulation comprising high molecular weight poly(ethylene oxide), an effective amount of a therapeutic compound and a plasticizer such as poly(ethylene glycol).

It is contemplated and within the scope of the present invention that the pharmaceutical formulation may be administered to a subject by any of a variety of methods known to the artisan.

It is also contemplated and within the scope of the present invention that the pharmaceutical formulation may comprise other components.

It is also contemplated and within the scope of the present invention that the process for preparing the pharmaceutical formulation may comprise multiple steps.

SUMMARY OF THE INVENTION

The present invention in some embodiments comprises a hot-melt extrudable controlled-release pharmaceutical formulation. This formulation is further described as comprising an effective amount of a therapeutic compound and a high molecular weight poly(ethylene oxide) homopolymer.

It should be understood that the particular combinations of therapeutic compound and PEO (of given molecular weight) will result in various formulations each possessing its particular combination of properties. As a result, one particular combination may be best suited for a first therapeutic compound while another combination may be best suited for a second therapeutic compound. Methods for the selection of a particular therapeutic compound / PEO (of a given molecular weight) combination follow below.

Other embodiments of the present invention further comprise a plasticizer. The particular combinations of therapeutic compound/ plasticizer/ PEO (of given molecular weight) will result in various formulations each possessing its particular combination of physical properties. As a result, one particular combination may be best suited for a first therapeutic compound while another combination may be best suited for a second therapeutic compound. Methods for the selection of a particular therapeutic compound / plasticizer/ PEO (of a given molecular weight) combination follow below.

Turning to another embodiment of the present invention, a process for preparing a controlled-release pharmaceutical formulation comprising a therapeutic compound and a high molecular weight poly(ethylene oxide) homopolymer is disclosed. The process in some embodiments comprises hot-melt extruding a pharmaceutical

formulation comprising a therapeutic compound and a high molecular weight poly(ethylene oxide) homopolymer.

Other embodiments of the present controlled-release pharmaceutical formulations comprise a therapeutic compound and a high molecular weight poly(ethylene oxide) homopolymer, where the formulation is prepared by hot-melt extruding a mixture of its components.

In some embodiments, the pharmaceutical formulation of the invention may contain more than one therapeutic compound as well as other components. These pharmaceutical formulations may be used in either a sustained, extended, controlled, timed or other equivalent release dosage form.

Other features, advantages and embodiments of the invention will be apparent to those skilled in the art from the following description, accompanying data and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1. Release profile of chlorpheniramine maleate from extruded pellets based on poly(ethylene oxide) of different molecular weights.

Fig. 2. Release profile of chlorpheniramine maleate from extruded pellets based on poly(ethylene oxide) (1,000,000 MW avg.) and different amounts of poly(ethylene glycol) plasticizer.

Fig. 3. Release profile of chlorpheniramine maleate from extruded 300 mg pellets containing poly(ethylene oxide) (80 - 94% wt., MW 1,000,000 MW avg.) and chlorpheniramine maleate (6 - 20% wt.).

DETAILED DESCRIPTION OF THE INVENTION

The use of hot-melt extrudable high molecular weight PEO for the preparation of pharmaceutical formulations has several advantages. The one-step process presented as part of the invention also provides therapeutic formulations with minimal thermal degradation of either the therapeutic compound or the PEO.

POLY(ETHYLENE OXIDE)

As used herein, the term "poly(ethylene oxide)" includes all polymers which are comprised of repeating units of ethylene oxide. High molecular weight PEO is generally described as having an average molecular weight of from about 1,000,000 to about 10,000,000. The poly(ethylene oxides) comprising the present formulation are available commercially from sources such as Union Carbide Corporation. The amount of PEO used in the formulation will depend upon its average molecular weight, physical properties, interaction with other components of the formulation, ability to solubilize the therapeutic compound, ease of formulation extrudability, the pharmacological activity of the therapeutic compound, the indication being treated, the targeted dosing regimen, the projected method of administration, the integrity or stability of the final formulation, desired release profile or other such reasons. Generally, PEO content will not exceed about 99.99% wt. of the formulation.

The average molecular weight of the PEO employed will generally affect the processing conditions selected. A very high average molecular weight PEO, such as greater than about 5,000,000, will generally require higher processing temperature, torque and/or pressure than a PEO having an average molecular weight less than or equal to about 5,000,000. Antioxidants and/or plasticizers may be advantageously employed when preparing the formulation of the invention. Thus, although not required to obtain a hot-melt extrudable formulation, addition of one or more plasticizers and/or antioxidants to the formulation will generally facilitate the preparation process.

As shown in Figure 1, PEO average molecular weight also affects the release profile of the formulation. Generally, increasing average molecular weight decreases release rate of therapeutic compound.

PLASTICIZERS

As used herein, the term "plasticizer" includes all compounds capable of plasticizing high molecular weight PEO. The plasticizer should be able to increase the space between chains and chain mobility of the PEO polymer melt in order to allow for lower processing temperature, extruder torque and pressure during the hot-melt extrusion process. PEG and Dow molecular weight PEO can help the processing by broadening the molecular weight distribution of the polymer blend. Plasticizers also generally reduce the viscosity of a polymer melt thereby allowing for lower processing temperature and extruder torque during hot-melt extrusion. It is possible the plasticizer

will impart some particularly advantageous physical properties to the pharmaceutical formulation of PEO.

As used herein, the term "low molecular weight PEO" is intended to mean poly(ethylene oxide) homopolymer having an average molecular weight less than about 500,000.

Plasticizers are not required in order to practice the invention. Their addition to the formulation is contemplated as being within the scope of the invention. Plasticizers are advantageously included when very high molecular weight PEO, such as greater than about 5,000,000, is employed.

As shown in Figure 2, it is possible that including a plasticizer in the present formulation will alter its release profile. Generally, increasing the amount of plasticizer present will increase the release rate of the therapeutic compound.

It is contemplated and within the scope of the invention, that a combination of plasticizers may be used in the present formulation. One advantageous combination is that comprised of poly(ethylene glycol) and low molecular weight poly(ethylene oxide).

The plasticizer employed herein may be a solvent for the PEO at the temperature at which the formulation is prepared. Such plasticizer, when mixed with the PEO above a characteristic temperature at which the PEO becomes soluble therein, may dissolve the PEO. Upon cooling, the mixture forms a matrix having especially useful properties for use in a sustained release dosage form.

Plasticizers useful in the invention include, by way of example and without limitation, low molecular weight polymers, oligomers, copolymers, oils, small organic molecules, low molecular weight polyols having aliphatic hydroxyls, ester-type plasticizers, glycol ethers, poly(propylene glycol), multi-block polymers, single block polymers, low molecular weight poly(ethylene oxide) (average molecular weight less than about 500,000) and poly(ethylene glycol).

Such plasticizers may be ethylene glycol, propylene glycol, 1,2-butylene glycol, 2,3-butylene glycol, styrene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol and other poly(ethylene glycol) compounds, monopropylene glycol monoisopropyl ether, propylene glycol monoethyl ether, ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, triethyl citrate, acetyl triethyl citrate, tributyl citrate and allyl glycolate.

All such plasticizers are commercially available from sources such as Aldrich or Sigma Chemical Co.

The PEG based plasticizers are available commercially or may be made by a variety of methods, such as disclosed in *Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications* (J.M. Harris, Ed.; Plenum Press, NY) the teachings of which are hereby incorporated by reference.

The amount of plasticizer used in the formulation will depend upon its composition, physical properties, effect upon the PEO, interaction with other components of the formulation, ability to solubilize the therapeutic compound or other such reasons. The amount of plasticizer present in the formulation affects its properties. Generally, when the plasticizer is PEG, its content will generally not exceed about 40% wt. of the formulation.

When present, the relative amount of plasticizer used may be expressed by the ratio high molecular weight PEO % wt.:plasticizer % wt. and will generally fall in the range of about 100:0 to about 60:40. The amount of plasticizer will generally not exceed the amount of PEO.

THERAPEUTIC PREPARATIONS

As used herein, the term "therapeutic compound is taken to mean an organic chemical substance having desired beneficial and therapeutic effects in mammals. Such compounds are generally classified as pharmaceuticals or biologicals. As long as the therapeutic compound can diffuse from the formulation when exposed to a biological fluid, its structure is not especially critical.

The therapeutic compounds contemplated within the scope of the invention include hydrophobic, hydrophilic and amphiphilic compounds. They may be in their free acid, free base, or pharmaceutically acceptable salt forms. They may be derivatives or prodrugs of a given pharmaceutical.

It will be appreciated that certain therapeutic compounds used in the present invention may contain an asymmetrically substituted carbon atom, and may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. Also, it is realized that cis and trans geometric isomers of the

therapeutic compounds are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

It is not necessary for the therapeutic compound to be soluble in any given formulation component. The therapeutic compound may be either dissolved, partially dissolved or suspended in the polymer matrix of the formulation. It is necessary for the therapeutic compound to be stable to the hot-melt extrusion process conditions used. By stable is meant that a significant portion of the therapeutic compound will not be degraded or decomposed throughout the hot-melt extrusion process.

The therapeutic compounds which may be hot-melt extruded in the formulation of the invention may be used for treating indications such as, by way of example and without limitation, inflammation, gout, hypercholesterolemia, microbial infection, AIDS, tuberculosis, fungal infection, amoebic infection, parasitic infection, cancer, tumor, organ rejection, diabetes, heart failure, arthritis, asthma, pain, congestion, urinary tract infections, vaginal infection, seizure related disorder, depression, psychosis, convulsion, diabetes, blood coagulation, hypertension and birth control.

The following therapeutic compounds can be administered by the pharmaceutical formulation of the present invention:

(1) analgesics such as aspirin, acetaminophen, deflunisal and the like;

(2) anesthetics such as lidocaine, procaine, benzocaine, xylocaine and the like;

(3) antiarthritics and anti-inflammatory agents such as phenylbutazone, indomethacin, sulindac, dexamethasone, ibuprofen, allopurinol, oxyphenbutazone probenecid, cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, triamcinolone, indomethacin, sulindac and its salts and corresponding sulfide and the like;

(4) antiasthma drugs such as theophylline, ephedrine, beclomethasone dipropionate, epinephrine and the like;

(5) urinary tract disinfectives such as sulfamethoxazole, trimethoprim, nitrofurantoin, norfloxicin and the like;

(6) anticoagulants such as heparin, bishydroxy coumarin, warfarin and the like;

(7) anticonvulsants such as diphenylhydantoin, diazepam and the like;

(8) antidepressants such as amitriptyline, chlordiazepoxide, perphenazine, protriptyline, imipramine, doxepin and the like;

(9) antidiabetics such as insulin, tolbutamide tolazamide, somatotropin, acetohexamide, chlorpropamide and the like;

(10) antineoplastics such as adriamycin, fluouracil, methotrexate, asparaginase and the like;

(11) antipsychotics such as prochlorperazine, lithium carbonate, lithium citrate, thioridazine, molindone, fluphenazine, trifluoperazine, perphenazine, amitriptyline, triflupromazine and the like;

(12) antihypertensives such as spironolactone, methyldopa, hydralazine, clonidine, chlorothiazide, deserpidine, timolol, propranolol, metaprotol, prazosin hydrochloride, reserpine and the like;

(13) muscle relaxants such as mephalan, danbrolene, cyclobenzaprine, methocarbamol, diazepam, succinoyl chloride and the like;

(14) antiprotozoals such as chloramphenicol, chloroquine, trimethoprim and sulfamethoxazole;

(15) spermicidals such as nonoxynol;

(16) antibacterial substances such as beta-lactam antibiotics, tetracyclines, chloramphenicol, neomycin, cefoxitin, thienamycin, gramicidin, bacitracin, sulfonamides, aminoglycoside antibiotics, tobramycin, nitrofurazone, nalidixic acid and analogs and the antimicrobial combination of fludalanine/pentizidone;

(17) antihistamines and decongestants such as perilamine, chlorpheniramine, tetrahydrozoline and antazoline;

(18) antiparasitic compounds such as ivermectin; and

(19) antiviral compounds such as acyclovir and interferon. For treatment of vaginal and urethral conditions requiring antifungal, amoebicidal, trichomonacidal agents or antiprotozoals, the following agents can be used: polyoxyethylene nonylphenol, alkylaryl sulfonate, oxyquinoline sulfate, miconazole nitrate, sulfanilamide, candicidin, sulfisoxazole, nysatitin, clotrimazole, metronidazole and the like.

Loading of the therapeutic compounds into the final formulation may be accomplished following the techniques below. Generally, the therapeutic compound is

loaded by premixing it with PEO and any other formulation components and hot-melt extruding the mixture. The mixture may be either a solution, slurry, suspension or solid. When solids are present in the mixture, they may be, by way of example and without limitation, either powdered, crystalline, amorphous, pelletized, beaded, spheronized, granular or the like.

It should be understood that the amount of therapeutic compound loaded into the formulation may be varied according to, for example, the high molecular weight PEO:therapeutic compound or the high molecular weight PEO:plasticizer:therapeutic compound ratios used in the pre-extruded mixture. Although a given loading method may be optimal for a particular high molecular weight PEO:therapeutic compound combination, all of the described methods will generally result in compound loading to some degree.

The therapeutic amount of compound loaded into the formulation will vary according to the pharmacological activity of the compound, the indication being treated, the targeted dosing regimen, the projected method of administration, the integrity or stability of the final formulation or other such reasons.

As shown in Figure 3, the amount of therapeutic compound loaded into the formulation will generally have only a marginal effect upon the release profile of therapeutic compound. In this particular embodiment, a 300 mg tablet contained high molecular weight PEO (about 60, or about 80 - to about 90, or about 94% wt., MW 1,000,000) and chlorpheniramine maleate (about 5, or about 6 - to about 20% wt.). The formulation was prepared following the procedure described in Example 3, and the release profile was determined following the procedure described in Example 1. In some embodiments, the compound loading into the formulation of the invention will not exceed about 20% wt. of the final formulation.

HOT-MELT EXTRUSION PROCESS

As used herein, the term "hot-melt extrudable" refers to a compound or formulation that may be hot-melt extruded. A hot-melt extrudable polymer is one that is sufficiently rigid at standard ambient temperature and pressure but is capable of deformation or forming a semi-liquid state under elevated heat or pressure. Although the formulation of the invention need not contain a plasticizer to render it hot-melt

extrudable, plasticizers of the type described herein may be included and still remain within the scope of the invention.

Although, the process referred to above has been called a hot-melt extrusion, other equivalent processes such as injection molding, hot dipping, melt casting and compression molding may be used. By using either of these methods, the formulation may be shaped as needed according to the desired mode of administration, e.g. tablets, pills, lozenges, suppositories and the like.

The hot-melt extrusion process preferably employed is conducted at an elevated temperature, i.e. the heating zone(s) of the extruder is above room temperature (about 20 °C). It is important to select an operating temperature range that will minimize the degradation or decomposition of the therapeutic compound during processing. The operating temperature range is generally in the range of from about 60° C to about 160° C as determined by the setting for the extruder heating zone(s).

In some embodiments of the invention, the hot-melt extrusion may be conducted employing a slurry, solid, suspension, liquid, powdered or other such feed comprising PEO and a therapeutic compound. Dry feed is advantageously employed in the process of the present invention.

The hot-melt extrusion process is generally described as follows. An effective amount of a powdered therapeutic compound is mixed with a high molecular weight PEO, and in some embodiments, with a plasticizer such as PEG. Other components may be added in the various embodiments of the invention. In some embodiments, the therapeutic compound:PEO ratio is generally about 0.01:about 99.99 to about 20:about 80% wt. depending on the desired release profile, the pharmacological activity and toxicity of the therapeutic compound and other such considerations. The mixture is then placed in the extruder hopper and passed through the heated area of the extruder at a temperature which will melt or soften the PEO and/or plasticizer, if present, to form a matrix throughout which the therapeutic compound is dispersed. The molten or softened mixture then exits via a die, or other such element, at which time, the mixture (now called the extrudate) begins to harden. Since the extrudate is still warm or hot upon exiting the die, it may be easily shaped, molded, chopped, ground, molded, spheronized into beads, cut into strands, tableted or otherwise processed to the desired physical form.

The extruder used to practice the invention may be any such commercially available model equipped to handle dry feed and having a solid conveying zone, one or multiple heating zones, and an extrusion die. A two stage single screw extruder, such as that manufactured by C.W. Brabender Instruments Incorporated (NJ) is one such apparatus. It is particularly advantageous for the extruder to possess multiple separate temperature controllable heating zones.

Many conditions may be varied during the extrusion process to arrive at a particularly advantageous formulation. Such conditions include, by way of example, formulation composition, feed rate, operating temperature, extruder screw RPM, residence time, die configuration, heating zone length and extruder torque and/or pressure. Methods for the optimization of such conditions are known to the skilled artisan.

When very high molecular weight PEO, such as greater than about 5,000,000, is employed, the hot-melt extrusion may require higher processing temperature, pressure and/or torque than when PEO having a molecular weight less than or equal to about 5,000,000 is employed. By including a plasticizer, and, optionally, an antioxidant, in a formulation comprising very high molecular weight PEO, processing temperature, pressure and/or torque may be reduced.

The following abbreviations are used in the description of the invention:

EO	ethylene oxide;
GPC	gel permeation chromatography;
MW	molecular weight;
PEO	poly(ethylene oxide); and
PEG	poly(ethylene glycol).

Following long-standing patent law convention, the terms "a" and "an" mean "one or more" when used in this application, including the claims.

PHARMACEUTICAL COMPOSITIONS AND THEIR ADMINISTRATION

The pharmaceutical formulation of the present invention may be administered by a variety of methods. Such methods include, by way of example and without limitation: oral, nasal, buccal, rectal, ophthalmic, otic, urethral, vaginal, or sublingual

dosage administration. Such methods of administration and others contemplated within the scope of the present invention are known to the skilled artisan.

In vivo stability of the present formulation may vary according to the physiological environment to which it is exposed and the specific therapeutic compound, PEO and plasticizer used. Therefore, the necessity for or frequency of readministration may be different for various formulations.

The pharmaceutical formulation of the present invention may be provided in a variety of ways. Additional components that would not significantly prohibit the hot-melt extrusion process may be added to the formulation prior to hot-melt extrusion. The additional components would still allow for the high molecular weight PEO:therapeutic compound mixture to be formulated using a hot-melt extrusion process.

For nasal administration, the pharmaceutical formulation may be a paste, cream or ointment containing the appropriate solvents (such as water, aqueous, nonaqueous, polar, nonpolar, hydropic, hydrophilic and/or combinations thereof) and optionally other compounds (stabilizers, perfumes, antimicrobial agents, antioxidants, pH modifiers, surfactants and/or bioavailability modifiers). It is contemplated that bioavailability enhancers such as alcohols or other compounds that enhance the penetration of the therapeutic compound from the pharmaceutical formulation into the nasal mucosa may be needed to prepare suitable formulations for nasal administration.

For oral, buccal, and sublingual administration, the pharmaceutical formulation may be in the form of a gel cap, caplet, tablet, capsule, suspension or powder. For rectal administration, the pharmaceutical formulation may be in the form of a suppository, ointment, enema, tablet or cream for release of compound into the intestines, sigmoid flexure and/or rectum.

In solid unit dosage forms, the compounds can be combined with conventional carriers, for example: binders, such as acacia, corn starch or gelatin; disintegrating agents, such as, corn starch, guar gum, potato starch or alginic acid; lubricants, such as, stearic acid or magnesium stearate; and inert fillers, such as lactose, sucrose or corn starch.

In some embodiments of the invention, the term "unit dosage form" is used herein to mean a single or multiple dose form containing a quantity of the therapeutic compound containing formulation, said quantity being such that one or more

predetermined units may be provided as a single therapeutic administration. In the case of multiple dose forms, such as suspensions or scored tablets, said predetermined unit will be one fraction of a prescribed full dosage regimen, i.e. a 5 ml (teaspoon) quantity of a prescribed 100 mL suspension.

The pharmaceutical formulations may also be administered as solutions or liquid suspensions comprising high molecular weight PEO, a therapeutic compound and a sterile liquid, such as an oil, water, an alcohol, or mixtures thereof, with or without the addition of a pharmaceutically suitable surfactants, suspending agent, or emulsifying agent for oral or parenteral administration.

For suspension preparations, the pharmaceutical formulation may include oils, for example, fixed oils, such as peanut oil, sesame oil, cottonseed oil, corn oil and olive oil; fatty acids, such as oleic acid, stearic acid and isotearic acid; and fatty acid esters, such as ethyl oleate, isopropyl myristate, fatty acid glyceridees and acetylated fatty acid glycerides. They may also be mixed with alcohols, such as ethanol, isopropanol, hexadecyl alcohol, glycerol and propylene glycol; with glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol; with ethers, such as poly(ethyleneglycol) 450, with petroleum hydrocarbons, such as mineral oil and petrolatum; with water, or with mixtures thereof; with or without the addition of a pharmaceutically suitable surfactant, suspending agent or emulsifying agent.

Oils can also be employed in the preparation of formulations of the soft gelatin type and suppositories. Water, saline, aqueous dextrose and related sugar solutions, and glycerols may be employed in the preparation of suspension formulations which may suitably contain suspending agents, such as pectin, carbomers, methyl cellulose, hydroxypropyl cellulose or carboxymethyl cellulose, as well as buffers and preservatives. Soaps and synthetic detergents may be employed as surfactants and as vehicles for detergent compositions. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts. Suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl and olefin sulfonates, alkyl, olefin, ether and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene)-*block*-poly(oxypropylene) copolymers; and amphoteric detergents,

for example, alkyl -aminopropionates and 2-alkylimidazoline quaternary ammonium salts; and mixtures thereof.

It is contemplated that either one or a combination of long-acting, sustained release, controlled release or slow release dosage forms may be used in the present invention. The course and duration of administration of and the dosage requirements for the formulation of the present invention will vary according to the subject being treated, the compound being administered, the formulation used, the method of administration used, the severity and type of indication being treated, the coadministration of other drugs and other factors.

The therapeutic compounds contained within the formulation may be formulated as their pharmaceutically acceptable salts. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent therapeutic compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfonic, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as amino acids, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent therapeutic compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a predetermined amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Generally, nonaqueous media are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Some embodiments of the invention comprise a hot-melt extrudable controlled release pharmaceutical formulation comprising an effective amount of a therapeutic compound, high molecular weight poly(ethylene oxide) and a plasticizer,

the poly(ethylene oxide) having a molecular weight average in the range of from about 1,000,000 to about 10,000,000.

In other embodiments, the invention provides a hot-melt extrudable controlled release pharmaceutical formulation comprising an effective amount of a therapeutic compound, high molecular weight poly(ethylene oxide) and a plasticizer,

the poly(ethylene oxide) having a molecular weight average in the range of from about 1,000,000 to about 10,000,000;

the poly(ethylene oxide):therapeutic compound ratio being in the range of from about 99.99:01 to about 80:20 % wt.; and

the plasticizer being selected from the group consisting of:

low molecular weight polymers, oligomers, or copolymers, oils, small organic molecules, low molecular weight polyols having aliphatic hydroxyls, ester-type plasticizers, glycol ethers, poly(propylene glycol), multi-block polymers, single block polymers, low molecular weight poly(ethylene oxide) (molecular weight less than about 500,000) and poly(ethylene glycol).

In other embodiments, the invention provides a hot-melt extrudable controlled release pharmaceutical formulation comprising an effective amount of a therapeutic compound, high molecular weight poly(ethylene oxide) and a plasticizer,

the poly(ethylene oxide) having a molecular weight average in the range of from about 1,000,000 to about 7,000,000;

the poly(ethylene oxide):therapeutic compound ratio being

in the range of from about 99.99:0.01 to about 80:20 % wt.;

the plasticizer being poly(ethylene glycol); and

the poly(ethylene oxide):poly(ethylene glycol) ratio being

in the range of from about 99.99:0.01 to about 60:40 % wt.

In other embodiments, the present invention provides a hot-melt extrudable controlled release pharmaceutical formulation comprising an effective amount of a therapeutic compound and high molecular weight poly(ethylene oxide),

the poly(ethylene oxide) having a molecular weight average in the range of from about 1,000,000 to about 10,000,000; and

the formulation being made by hot-melt extruding the therapeutic compound and the high molecular weight poly(ethylene oxide).

Unless otherwise indicated, all chemicals were purchased from Aldrich Chemicals (Milwaukee, WI).

EXAMPLE 1
Method For The Determination Of Therapeutic Compound Release Rate

The therapeutic compound release rate was generally determined as follows and as described in USP 23 NF18 (pages 1791-1792), method 711, apparatus II. The formulation was placed in water (100 mL at 37 °C) in a flask while stirring to form a dilute suspension. Aliquots of the suspension solution were drawn from the flask at intervals and filtered to remove suspended solids. The supernatant was then analyzed by HPLC and the concentration of therapeutic compound in solution quantified. By repeating this procedure, the release profile for various formulations was determined.

EXAMPLE 2
Preparation Of A Therapeutic Compound/ Poly(ethylene oxide) Formulation

A known amount of losoxanthrone solid is mixed with a known amount of PEO polymer. The weight ratio of losoxanthrone:polymer is 5:95% wt. The solid mixture is placed in an extruder hopper. The extruder has a solids conveying mechanism which extends from the hopper through a heating zone to the extrusion die. The solid mixture is passed through the heated extruder at a temperature range of about 100° to about 140° C, as determined by the temperature setting of the extruder heating zone so that melting or softening of the PEO occurs. Upon exiting the die, the extrudate (PEO/losoxanthrone) is chopped to the desired length. The extrudate is then either ground to a powder or molded to a caplet prior to final formulation.

EXAMPLE 3
Preparation of A Therapeutic Compound/Poly(ethylene oxide)Formulation

Chlorpheniramine maleate (9.6 g) was mixed with poly(ethylene glycol) (32.0 g, molecular weight average 3.350) in a twin-shell blender for five minutes. Poly(ethylene oxide) (118.4 g, molecular weight average 1,000,000) was then added and the entire mixture stirred for 10 minutes. The solid mixture was placed in an extruder hopper. The extruder had a single screw solids conveying mechanism which extended from the hopper through multiple heating zones to the extrusion die, the die having a 1 cm diameter. The solid mixture was passed through the heated extruder at a temperature range of about 75 to about 130° C, as determined by the temperature setting of the extruder heating zones so that melting or softening of the PEO occurred. An extruder torque of 34 (Nm) and screw speed of 25 r.p.m. were used. Upon exiting the die, the extrudate was chopped to form tablets 0.6 cm thick. The release rate profile of cpm was determined for the formulation using the method of Example 1.

EXAMPLE 4
Preparation Of Various Therapeutic Compound/Poly(ethyleneoxide) Formulations

Various other formulations were prepared using the method of Example 3. The composition and processing conditions used for these formulations is summarized in the table below. The chlorpheniramine maleate concentration was kept constant at 6% wt. for the following examples. The amounts of PEO and PEG were varied. The molecular weight average of the PEG was kept constant at 3,350. The molecular weight average of the PEO was varied.

Composition		Heating Zone 1 Temp (deg C) Temp (deg C)	Heating Zone 2 Temp (deg C) Temp (deg C)	Die Temp (deg C) (deg C)	Torque (Nm))	Screw Speed (rpm)
PEG) (%wt)	PEO (%wt, MW)					
0	94, 1,000,000	110	115	130	34	25
6	88, 1,000,000	110	115	130	28	25
20	74, 1,000,000	70	75	85	23	25
40	54, 1,000,000	70	70	85	10	25
0	94, 7,000,000	135	140	145	35	25
20	74, 7,000,000	90	90	100	21	25

The above is a detailed description of particular embodiments of the invention. It is recognized that departures from the disclosed embodiment may be made within the scope of the invention and that obvious modifications will occur to a person skilled in the art. The full scope of the invention is set out in the claims that follow and their equivalents. Accordingly, the claims and specification should not be construed to unduly narrow the full scope of protection to which the invention is entitled.

REFERENCES

The following references, to the extent they provide exemplary procedural or other details supplementary to those set forth herein, are specifically hereby incorporated by reference.

1) G. Bechmann, Ueber die verzögerte Wirkstoff-Freigabe aus peroralen, festen Arzneiformen (Ph.D. Thesis, University of Frankfort, 1964);

2) El-Egakey et al., *Pharm. Acta. Helv.* (1971), 46, 31-52;

3) Hüttenrauch et al., *Pharmazie* (1975), 30, 229-233;

4) Rippie et al., *J. Pharm. Sci.* (1969), 58, 428-431;

5) Shivanand et al., *Pharm. Res.* (1991), 8, S-192;

6) Prapaitrakul et al., *Pharm. Res.* (1989), 6, S-98;

7) Mank et al., *Pharmazie* (1989), 44, 773-776;

8) Mank et al., *Pharmazie* (1990), 45, 592-593;

9) Follonier et al., *Drug Develop. and Indust. Pharm.*, (1994), 20(8), 1323-1339;

10) .C. Snipes, US 5,004,601;

11) US 4,806,337;

12) US 4,774,074;

13) US 4,774,976;

14) US 4,629,621;

15) Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications (J.M. Harris Ed., Plenum Press, NY);

16) Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Co., Easton, PA, 18042, 1985);

17) Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 7th ed. (A. Goodman Gilman, L.S. Goodman, T.W. Rall & F. Murad Ed.s, MacMillan Publishing Co., NY, 1985).

CLAIMS

What is claimed is:

1) A hot-melt extrudable controlled release pharmaceutical formulation comprising an effective amount of a therapeutic compound and a high molecular weight poly(ethylene oxide),

the poly(ethylene oxide) having a molecular weight average in the range of from about 1,000,000 to about 10,000,000 Daltons.

2) A hot-melt extrudable controlled release pharmaceutical formulation as described in Claim 1 further comprising a plasticizer.

3) A hot-melt extrudable controlled release pharmaceutical formulation as described in Claim 2, wherein:

the poly(ethylene oxide):therapeutic compound ratio is in the range of from about 99.99:01 to about 80:20 % wt.; and

the plasticizer is selected from the group consisting of: low molecular weight polymers, oligomers, or copolymers, oils, small organic molecules, low molecular weight polyols having aliphatic hydroxyls, ester-type plasticizers, glycol ethers, poly(propylene glycol), multi-block polymers, single block polymers, low molecular weight poly(ethylene oxide) (molecular weight less than about 500,000 Daltons) and poly(ethylene glycol).

4) A hot-melt extrudable controlled release pharmaceutical formulation comprising an effective amount of a therapeutic compound, high molecular weight poly(ethylene oxide) and a plasticizer,

the poly(ethylene oxide) having a molecular weight average

in the range of from about 1,000,000 to about 7,000,000 Daltons;

the poly(ethylene oxide):therapeutic compound ratio being in the range of from about 99.99:0.01 to about 80:20 % wt.;

the plasticizer being poly(ethylene glycol); and

the poly(ethylene oxide):poly(ethylene glycol) ratio being in the range of from about 99.99:0.01 to about 60:40 % wt.

5) A hot-melt extrudable controlled release pharmaceutical formulation comprising an effective amount of a therapeutic compound and high molecular weight poly(ethylene oxide),

the poly(ethylene oxide) having a molecular weight average in the range of from about 1,000,000 to about 10,000,000 Daltons; and

the formulation being made by hot-melt extruding the therapeutic compound and the high molecular weight poly(ethylene oxide).

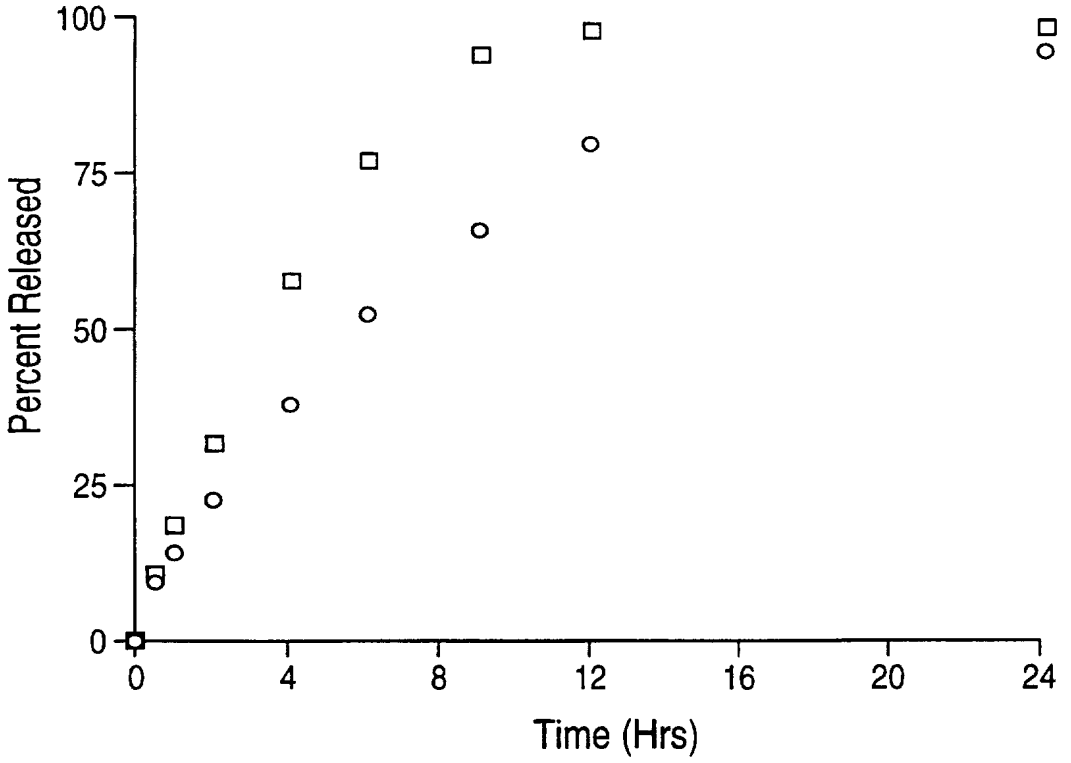
100
75
50
25
0
Percent Released
0
4
8
12
16
20
24
Time (Hrs)
o 6% CPM, 20% PEG (3,350), Polyethyleneoxide (7,000,000)
□ 6% CPM, 20% PEG (3,350), Polyethyleneoxide (1,000,000)

Fig. 1

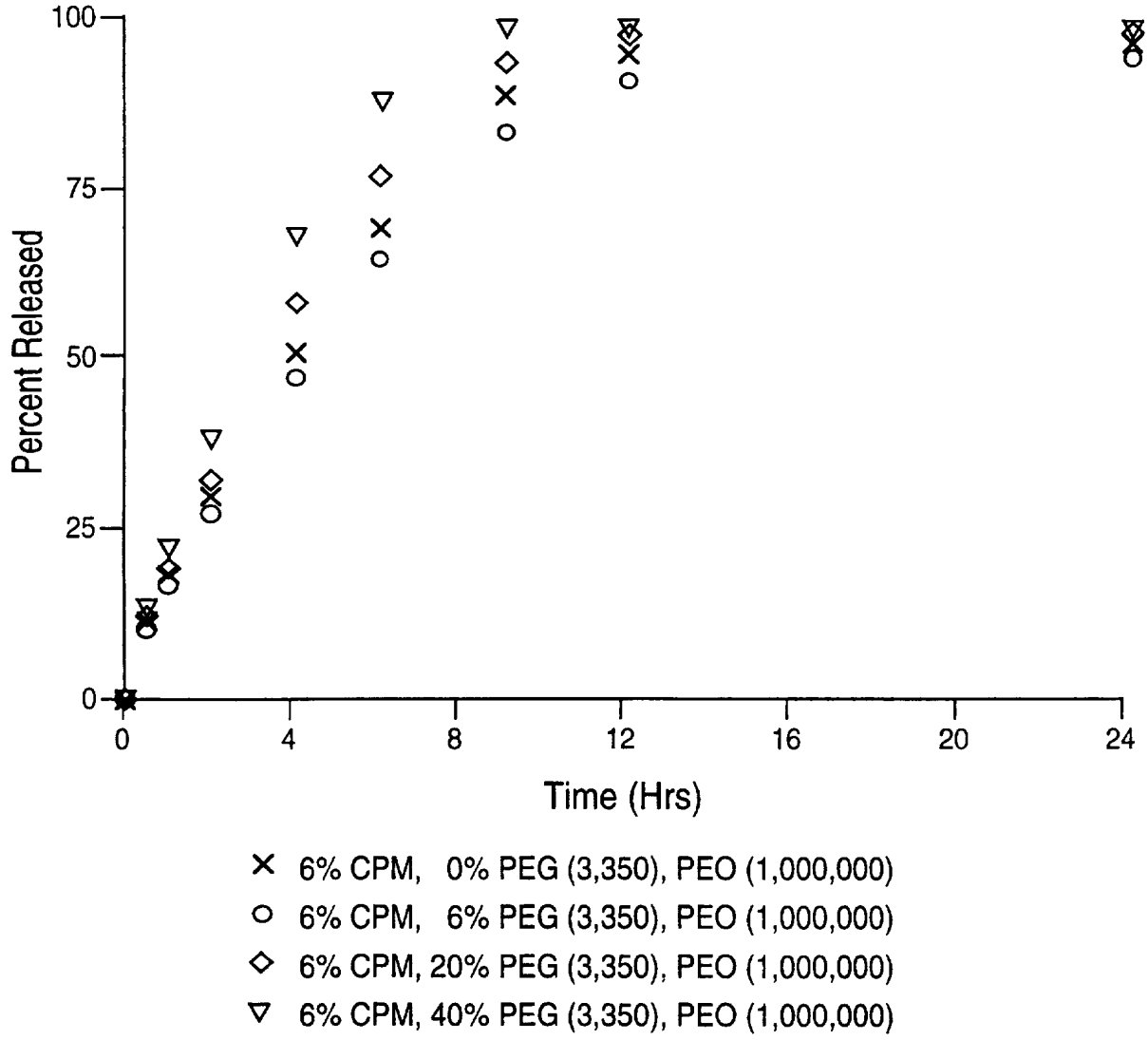
100
75
50
25
0
Percent Released
0
4
8
12
16
20
24
Time (Hrs)
6% CPM, 0% PEG (3,350), PEO (1,000,000)
6% CPM, 6% PEG (3,350), PEO (1,000,000)
6% CPM, 20% PEG (3,350), PEO (1,000,000)
6% CPM, 40% PEG (3,350), PEO (1,000,000)

Fig. 2

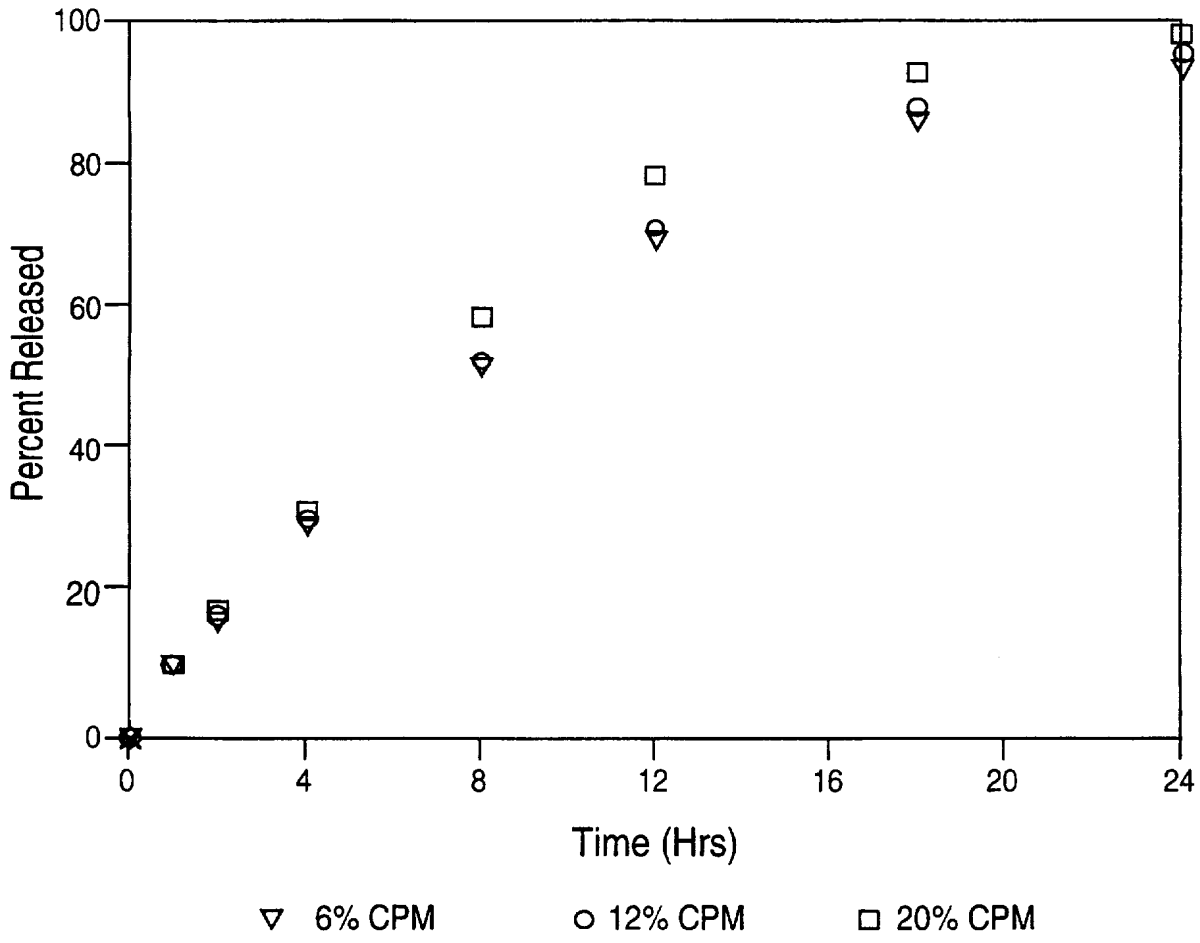
100
80
60
40
20
0
Percent Released
0
4
8
12
16
20
24
Time (Hrs)
6% CPM
12% CPM
20% CPM

Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/11206

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/10, 47/34
US CL :424/486; 514/772.3
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/486; 514/772.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,713,243 A (SCHIRALDI et al) 15 December 1987, see abstract and column 4, lines 24-38.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 15 AUGUST 1997	Date of mailing of the international search report 09 SEP 1997
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